



State of New Jersey

CHRIS CHRISTIE
Governor

KIM GUADAGNO
Lt. Governor

Department of Environmental Protection
Office of Science
Mail Code 428-01 P.O. Box 420
Trenton, NJ 08625-0420
(609) 984-6070
Fax (609) 292-7340

BOB MARTIN
Commissioner

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Dr. Lori White
NIEHS
P.O. Box 12233
MD K2-03
Research Triangle Park, NC 27709

Dear Dr. White,

I am submitting comments on the Draft Technical Report on the Toxicology and Carcinogenesis Study of Styrene-Acrylonitrile Trimer in F344/N Rats (Perinatal and Postnatal Feed Studies). I am a toxicologist with the New Jersey Department of Environmental Protection (NJDEP) with responsibility for human health risk assessment of drinking water contaminants. I have been a member of the SAN Trimer Interagency Work Group since it was established in 1997, as well as the internal NJDEP Toms Work Group which addressed issues related to drinking water contamination in Toms River/Dover Township, NJ.

I agree with the conclusions of the draft report, and my comments primarily focus on suggested clarifications.

Specific comments are:

- p. 6. Last line of first paragraph. Suggested change: The affected communities were exposed to SAN Trimer in the Reich Farm Superfund site's groundwater plume *through contamination of their drinking water wells*.
- p. 6. Final sentence. The comet and micronucleus assays should also be mentioned.
- p. 7, 59. First paragraph, last sentence. Can any more detail about the nature of the non-neoplastic lesions be provided?

p. 24. Toxicokinetic Studies, first sentence. Is anything known about the impurities in the radioactive SAN Trimer (19-27%)?

p. 27. Re: Peer-reviewer comment, “The F344/N rat model used by the NTP is probably appropriate for studying brain tumors, but the panel agreed that is it not a good model for leukemia because this strain has a high background rate of mononuclear cell leukemia.” Should this concern expressed by the peer reviewers be mentioned in the discussion of the leukemia incidence in this study?

p. 49. Genetic Toxicology, first sentence. All three organs/tissues tested in the comet assay were found to be targets for SAN Trimer toxicity in this study. The reason for selecting these three tissues should be discussed. Should a non-target tissue also have been tested for comparison?

p. 51. First two sentences. Micronucleus test. The predictivity of positive results in acute versus long-term micronucleus assays is discussed. In this study, the chemical was administered for 4 days for the micronucleus test. Is this considered acute or long-term exposure in the context of the micronucleus test?

p. 54, 60, 68. Fertility index, number of litters, and litter size. Is there a possible reason for effects on these parameters only in the 18 week study, but not at the same doses in the 7 week and 2 year studies?

p. 66, first sentence. It is suggested that it be stated that the absolute and/or relative organ weights increased in a dose-related fashion, when this is the case.

p. 79. Last paragraph, first sentence, first word. “The” should be changed to “They.”

p. 86. Genetic Toxicology. Second paragraph – explanation of comet assay results. Same comment also applies to related discussion in Results section on p. C-4. The basis for the conclusion that increases in DNA damage were greater in brain than in liver is not clear from the data presented in Table 20. The discussion of these results needs to be clarified.

The following explanation was provided to me in an email from Dr. Kristine Witt, NTP genetic toxicologist, to Dr. Raj Chhabra. A summary of this information should be included in the report:

“The actual values for DNA damage levels, particularly in female rat liver cells, are quite impressive. In females, the levels seen in the high dose samples actually approach the level of DNA damage induced in the positive control rats treated with ethyl methanesulfonate. I do agree that it appears that the responses seen in liver following treatment with SAN trimer are far stronger than the responses seen in brain tissue. However, due to the large variation (high standard errors) seen with the liver samples, the statistical analysis did not support a call of positive. We prefer to see both a significant trend test and at least one dose significantly elevated over the control in order to confidently conclude that a test is positive.

In the case of this study, in both male and female rats, the trend test for liver is significant (<0.025) but none of the doses is significantly increased over the vehicle control. Therefore, we don't consider the test to be positive in liver. NTP is being highly conservative in its statistical analysis methods. Other people are, of course, welcome to evaluate the data using other methods and reach different conclusions.

The results in liver and in blood support the results seen in brain, and altogether, the data strongly indicate that SAN trimer, under the conditions of this subacute exposure study, induced DNA damage in brain, liver, and blood leukocytes.”

Additionally, the results of the comet assay for the SAN trimer should be discussed in the context of the overall database for comet test results. A comprehensive review of the results of the comet assay in 208 chemicals included in the IARC monographs and/or NTP carcinogenicity databases (Sasaki et al. 2000. Crit. Rev. Toxicol. 30: 629-799) concludes that most target organs for carcinogenicity show positive results in the comet assay, but that many non-target organs also give positive results. Thus the comet assay cannot predict the target organs for carcinogenicity from the organs giving positive comet assay results. Also discussed is the fact that less than 50% of Ames-test negative rodent carcinogens were positive in the comet assay, while most Ames test negative rodent non-carcinogens were negative in the comet assay.

p. 92. First paragraph, second to last sentence about female rats. It should be mentioned that one nervous system tumor occurred in the control group of female rats.

p. 93. Second full sentence. Is it accurate to say that the incidence of brain/spinal cord neoplasms was marginally increased in females based on the incidence data? The data are 1/50, 2/50, 2/50, 0/50 in the control, low, mid, and high dose groups, respectively.

p. 94. First paragraph. Should it be mentioned that there were positive results for the *in vivo* genotoxicity assays in all of the organs/tissues selected for testing in this study?

p. 94. Last paragraph. It is stated that the CNS and PNS are the only targets of SAN Trimer toxicity in this study. This contradicts the statement in the Conclusions section on p. 95 and in the Conclusions of the Abstract (p. 10) where it is stated that lesions of the bone marrow, liver, and urinary bladder were also attributed to SAN Trimer exposure.

Thank you for the opportunity to comment on the draft report of this important study. I look forward to listening to the discussions of this study during the upcoming peer review meeting and to reading the final version of this report.

If you have any questions or need further information, please feel free to contact me at gloria.post@dep.state.nj.us or (609) 292-8497.

Sincerely,

Gloria B. Post, Ph.D., DABT
Research Scientist

C: Gary Buchanan, Office of Science, NJDEP
Karen Fell, Division of Water Supply, NJDEP
Sandra Krietzman, Division of Water Supply, NJDEP
Barry Frasco, Division of Site Remediation, NJDEP
Jerald Fagliano, NJ Department of Health and Senior Services
Marian Olsen, EPA Region 2